The Biologics License Application Process

An Overview

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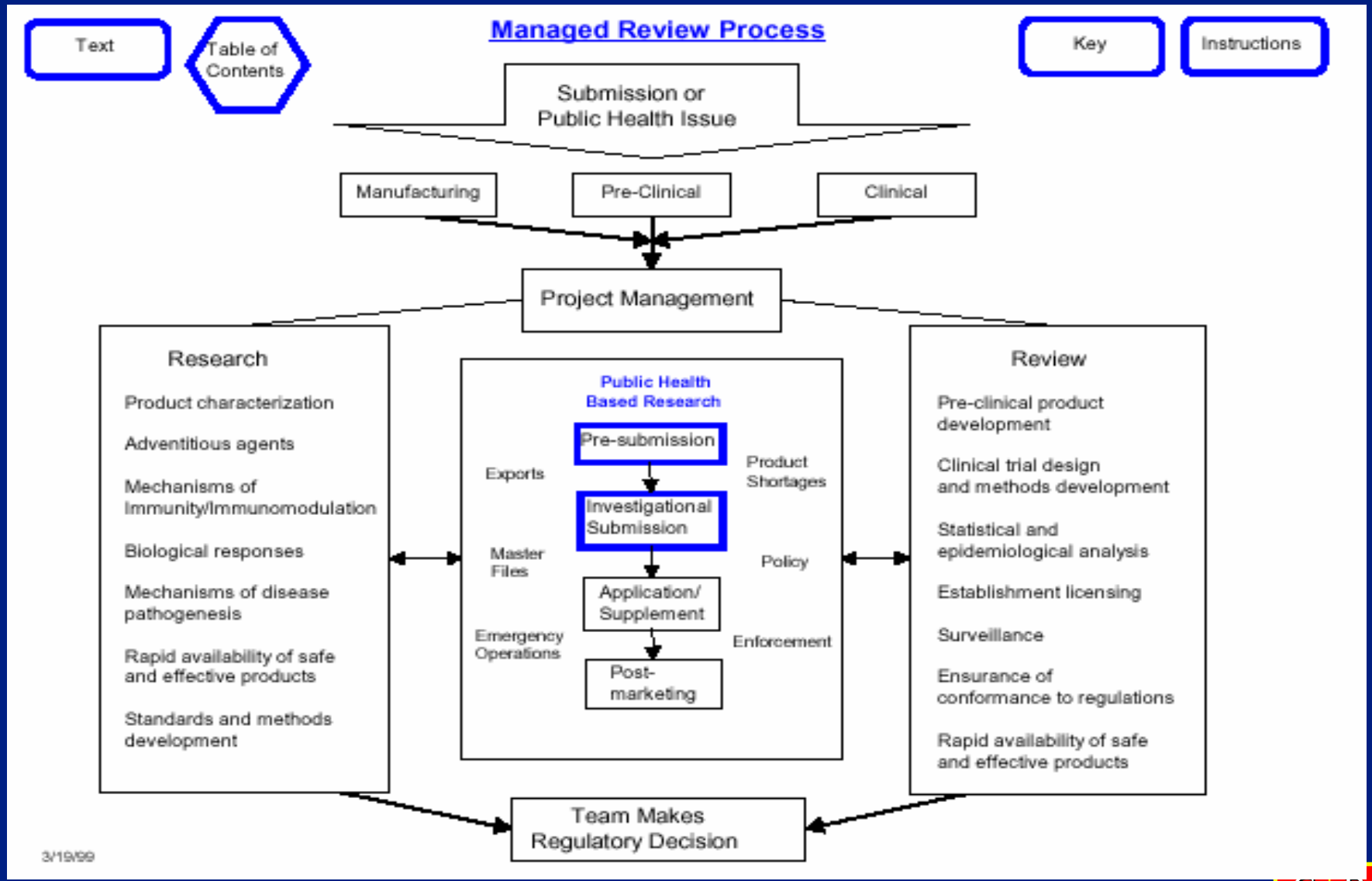
What is a Biologics License Application (BLA)?

A request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce

21 CFR 601.2

CBER Regulatory Authority

- **BIOLOGICS**
  - Investigational New Drug Exemptions (IND, 21 CFR 312)
  - Biologics License Applications (BLA, 21 CFR 600-680)
- **EXAMPLES**
  - Vaccines and allergenic products
  - Blood Products (including blood grouping reagents and donor screening tests for bloodborne pathogens)
  - Cellular & gene therapies, xenotransplantation)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Manufacturing
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Statistical and epidemiological analysis
Establishment licensing
Surveillance
Ensurance of conformance to regulations
Rapid availability of safe and effective products
Team Makes Regulatory Decision
3/19/99

Who Submits a BLA ?

MANUFACTURER (Applicant)

- Any legal person or entity who is engaged in manufacture

or

- An applicant for a license who takes responsibility for compliance with product and establishment standards

What is in a BLA?

- Form FDA 356h (cover sheet)
- Applicant Information
- Product / Manufacturing information
- Pre-clinical studies
- Clinical studies
- Labeling

BLA – Applicant Information

- Name, address & phone number
- Name & address of facilities
- Authorized official

BLA – Product/Manufacturing Information

- Source material / raw materials
- Manufacturing process and controls
- Formulation
- Facility information
- Contamination/cross-contamination information
- Environmental assessment or categorical exclusion

BLA – Safety, Efficacy and Use Information

- Pre-clinical studies
- Clinical studies
- Labeling

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International Harmonization

Using the CTD (Common Technical Document)

- **An agreed upon common format for the modular presentation of summaries, reports and data**
- **Content is harmonized to the extent of relevant ICH guidelines**
- **Guidance for Industry: Submitting Marketing Applications According to the ICH-CTD Format - General Considerations**
  - **http://www.fda.gov/cber/gdlns/mrktapich.pdf**

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CTD Format

- **Module 1: Regional Information**
  - Form 356h
  - Table of Contents (TOC)
  - administrative documents, including labeling
- **Module 2: Summaries**
  - Quality
  - Non-clinical (plus overview)
  - Clinical (plus overview)

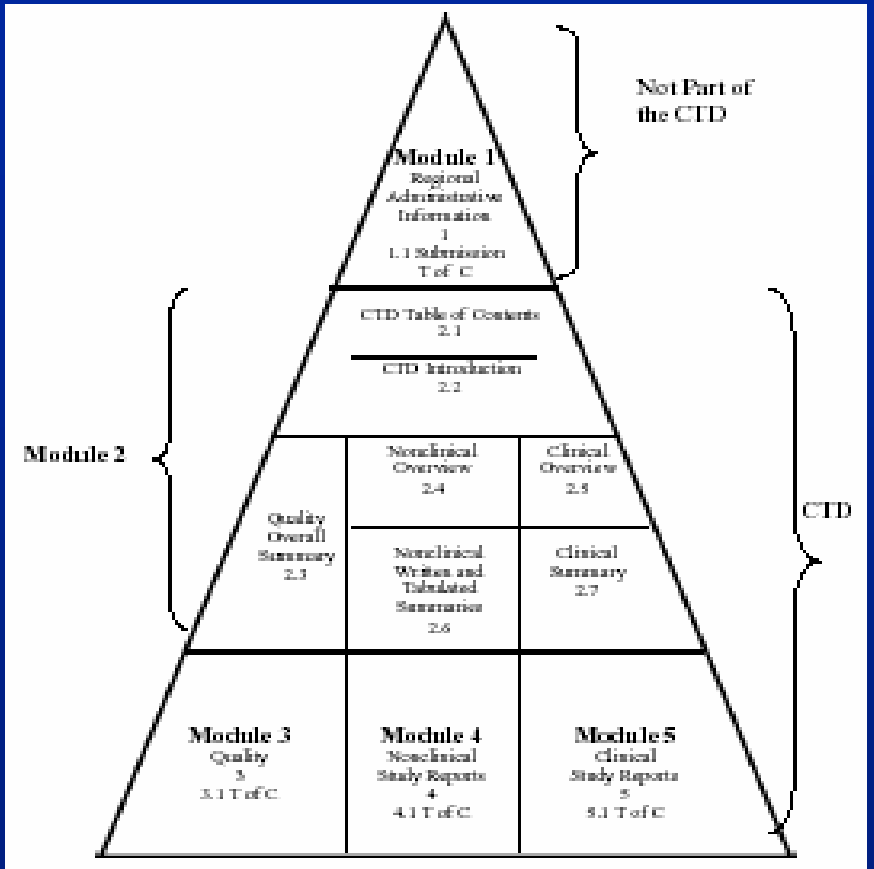
CTD Format

- **Module 3 Quality (CMC section)**
  - Table of Contents
  - Body of data
  - Literature references
- **Module 4 Nonclinical Study Reports**
  - Table of Contents
  - Study reports and related information
  - Literature References

CTD Format

- **Module 5 Clinical Study Reports**
  - Table of Contents
  - Study reports and related information
  - Literature References

Basic CTD Format



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Electronic Submissions

- **Submission of BLA/S may be made on paper or electronically**
- **Submissions should be made in accordance with published guidance:**
  - **http://www.fda.gov/cber/esub/esub.htm**

Before the BLA is Submitted

- Pre-BLA meeting
- Review committee already identified at first meeting with firm
- Consider Advisory Committee needs & scheduling issues
- Arrange for BiMo Inspection

Roles and Responsibilities of RPMs at Meetings

- **Application Divisions (RPMs)**
  - Ensure SOPP 8101.1 followed by team/sponsor
  - Update meeting database
  - Schedule internal pre-meeting to discuss meeting materials (as per MRP)
  - Handle meeting logistics (Room, phone, AV, etc.)
  - Ensure team issues meeting minutes by day 30

Roles and Responsibilities of Reviewers at Meetings

- **Laboratory (Review) Divisions:**
  - **Have appropriate disciplines represented**
  - **Resolve issues as possible at internal pre-meeting**
  - **Edit minutes to ensure accuracy**

FDA's Expectations of Applicants at Meetings

- **Work closely with the RPM to maximize meeting efficiency by following SOPP 8010.1**
  - **Pre-meeting materials**
    - **Provide on time**
    - **Concise, accurate, well labeled**
    - **Pose questions to be answered**
  - **Follow meeting agenda and timelines**

Good Review Management Principles

- Guidance issued April 2005
- http://www.fda.gov/cber/gdlns/reviewpdufa.htm
- Consistent with CBER Managed Review Process
- Obligates CBER to GRMP under Good Guidance Practices, I.e., deviations allowed only with supervisory approval (only when the specific situation warrants and the justification needs to be documented contemporaneously)

The Review Committee

CONSTITUTED TO CONTAIN THE NECESSARY EXPERTISE TO REVIEW THE SUBMISSION

Responsibilities – Chairperson/Lead

- **CONSTITUTE the committee**
- **ASSIGN sections for review**
- **SCHEDULE and CONDUCT meetings w/RPM**
- **REVIEW according to Managed Review and Good Review Management Principles**
- **WRITE “action” letters w/RPM**
- **PRESENT at Advisory Committee Meetings**
- **REQUEST a pre-license inspection**
- **PREPARE a Summary of Basis for Approval (SBA)**

Responsibilities
Regulatory Project Manager

- MANAGE the review of the application
- REVIEW assigned portions of application
- PERFORM QC check on the review process
- ASSURE reviews are documented properly
- ASSURE review of labeling is complete
- COORDINATE compliance status check
- PREPARE approval letter for new products
- PREPARE finding of no significant impact

Responsibilities Discipline Reviewer

- REVIEW assigned sections of the application
- WRITE a review memo, containing a summary, recommendation for action and letter-ready questions
- ATTEND and PARTICIPATE in review committee meetings following Good Review Management Principles and Managed Review Procedures
- COMMUNICATE with the applicant and document the discussion (as per Staff Manual Guide 2126.2)
- PREPARE for Advisory Committee meetings
- PARTICIPATE in the pre-approval inspection (if necessary)
- CONSIDER if a public health and/or research questions need to be answered relative to product approval

Application Received

- **Administrative processing**
  - Submission tracking number assigned (STN)
  - data entry
  - user fee verification
- **First committee meeting**
  - review assignments
  - time frames

SUBMISSION TRACKING NUMBER
aaaaaa.bbbb/cccc

Filing Review

- **Review for completeness**
  - **RTF policy**
  - **CBER SOPP 8404 Refusal to File Guidance for Product License Applications and Establishment License Applications**
- **Filing meeting**
- **Filing letter**
- **Communicate any significant deficiencies noted up to that time (but not a complete review) by day 74**

Refuse To File

- A refusal to file (RTF) letter is issued when the submission has been deemed not sufficiently complete for a meaningful review
- 21 CFR601.2(a), RTF Policy, SOPP 8404
- The Applicant may request that the submission be Filed Over Protest: SOPP 8404.1

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Complete Review

- **Substantive review (by review team or using cross office/center collaborative or consultative review)**
  - **Information requests**
  - **Discipline reviews (review templates under development)**
    - **Collaborative/consultative review: SOPPs 8001.1 & 8001.5**
  - **Review memos**
  - **Labeling**
  - **Lot release protocols**
- **Inspections**
  - **Facility**
  - **Bioresearch Monitoring**
- **Advisory Committee presentation**

Information Requests (IRs)

- Issued while the review is in progress
- Requests information needed to continue the review
- IRs may be made by letter, telephone or FAX
- IRs are documented in the file
- The response to an information request should not be so great as to constitute a major amendment
- Responses to information requests do not necessarily have to be reviewed in the current review cycle
- DOES NOT STOP THE REVIEW CLOCK
- SOPP 8401.1

Discipline Reviews (DRs)

- A DR letter is issued when a particular discipline (clinical, CMC, etc.) has finished its review, but the complete review is not yet done
- A DR letter contains comments and questions that might appear in the action letter
- Responses to DR letters need not necessarily be reviewed prior to issuance of the action letter
- DOES NOT STOP THE REVIEW CLOCK
- SOPP 8401.1

Administrative Record

- Paper trail documenting the decision making process and basis for the decision
- Copies of Telecons, FAXes, Review Memos, Meeting Minutes, etc., become part of the administrative record and are entered into the file and the tracking system

Action Decision

- **After a complete review is finished**
  - **Inspections**
  - **Advisory Committee**
- **Review Committee meeting**
  - **Outstanding issues**
  - **Agreements & commitments**
- **License action recommendation**
  - **Not ready for approval**
  - **Approval**

ACTION
Not Ready for Approval

- **COMPLETE RESPONSE LETTER**
  - Itemizes all deficiencies in the application that must be corrected prior to approval
  - Stops the review clock
- **RESUBMISSION**
  - Class 1 or 2
  - Restarts the clock

Dispute Resolution

- **Guidance for Industry: Formal Dispute Resolution: Appeals Above the Division Level**
- **SOPP 8005 Major Dispute Resolution Process (2/11/99)**

PDUFA Resubmissions

- Guidance for Industry: Classifying Resubmissions in Response to Action Letters, May 14, 1998
- SOPP 8405.1 Procedures for the Classification of Resubmissions of an Application for a Product Covered by PDUFA III

Performance Goals (con't)

Resubmitted Applications (Efficacy Supplements)

- Class 1
  - 90% in 2 months (90% in 4 mo.; 50 % in 2 mo.)
- Class 2
  - 90% in 6 months (90% in 6 mo.)
- Clinical Hold Responses
  - 90% in 30 days
- Major Dispute Resolution
  - 90% in 30 days
- Special Protocol Assessments
  - 90% in 45 days

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ACTION
Approval

- Compliance check
- Summary of Basis for Approval (SBA)
- Finding of No Significant Impact (FONSI) or confirm categorical exclusion
- Approval letter
  - Grants permission to distribute
  - Itemizes all agreements & commitments
- Issue license

How are processes/policies made?

- **Coordinating Committees meet**
  - **Composed of members from each affected office**
  - **Share information, propose solutions to cross-cutting problems, develop consensuses on issues**
  - **Issue guidances or SOPPs**
  - **Recommend policy to the Center Director for approval**

Coordinating Committees

- **Coordinating Committees**
  - Review Management (RMCC)
    - SOPPs, Review Processes, Records Management, Letter templates, other
  - Medical Products (MPCC)
    - Address medical issues, e.g., pediatrics, medical necessity, other
  - Information Management (IMCC)
    - Computer, email, internet, other support
  - Biologics Research (RRCC)
    - Research issues
  - Chemistry Manufacturing and Controls (CMC CC)
    - Stability, sterility, purity, mfg processes, other
  - Policy (PCC)
    - Laws, regulations, guidances
  - International Policy and Activities (IPACC)
    - International relations, agreements, standards

Rules of the Road for Reviewers

- SGRA
  - SOPPs
  - Guidances
  - Regulations
  - Acts